A Randomized Controlled Trial of Mometasone Furoate Nasal Spray for the Treatment of Nasal Polyposis

Pär Stjärne, MD, PhD; Ralph Mösges, MD, PhD; Mark Jorissen, MD, PhD; Desiderio Passàli, MD, PhD; Luisa Bellussi, MD, PhD; Heribert Staudinger, MD; Melvyn Danzig, MD

Objective: To evaluate the efficacy and safety of mometasone furoate nasal spray (NS) for the treatment of nasal polyposis.

Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter study.

Setting: A total of 24 centers in 17 countries.

Patients: A total of 310 subjects 18 years or older with bilateral nasal polyps.

Interventions: (1) A 200-µg dose of mometasone furoate NS in the morning and matching placebo in the evening; (2) 200-µg doses of mometasone furoate NS in the morning and evening; or (3) matching placebo in the morning and evening. All 3 regimens were administered as a nasal spray for 4 months.

Main Outcome Measures: Primary end points were change from baseline to last assessment in physician-assessed bilateral polyp grade and change from baseline in subject-assessed congestion and/or obstruction score averaged over the first month of treatment. Analysis of variance was used for all efficacy end points except for change in bilateral polyp grade, for which baseline polyp grade was added as a covariate to the analysis of variance model to account for any between-group baseline differences in this variable.

Results: Mometasone furoate NS doses of 200 µg administered once or twice daily produced greater reductions in bilateral polyp grade at the end point than placebo, with differences reaching statistical significance with twice-daily dosing ($P = .04$). Over 1 month, both mometasone furoate NS regimens produced statistically superior improvements from baseline in congestion and/or obstruction score vs placebo ($P = .01$ for once-daily dosing; $P < .001$ for twice-daily dosing). The drug was well tolerated.

Conclusion: Mometasone furoate NS is an effective and well-tolerated treatment for bilateral nasal polyposis in adults, reducing nasal polyp size and symptoms of nasal congestion and/or obstruction.

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Author Affiliations:
Department of Otorhinolaryngology, Karolinska University Hospital, Stockholm, Sweden (Dr Stjärne); Institute of Medical Statistics, Informatics, and Epidemiology, University of Cologne, Cologne, Germany (Dr Mösges); Department of Otorhinolaryngology–Head and Neck Surgery, University Hospital Leuven, Leuven, Belgium (Dr Jorissen); Department of Otorhinolaryngology, University of Siena, Siena, Italy (Drs Passàli and Bellussi); and Schering-Plough Research Institute, Kenilworth, NJ (Drs Staudinger and Danzig).

NASAL POLYPS ARE BENIGN growths of the nasal mucosa associated with edema, fibrosis, reduced vascularization, a decreased number of glands and nerve endings, and damaged epithelium.[1,2] The cause of nasal polyposis is not completely understood; however, it is frequently associated with asthma and intolerance to aspirin.[3] The condition is thought to be a result of underlying mucosal disease[4] and is characterized by eosinophil inflammation: approximately 65% to 90% of polyps are classified histologically as eosinophilic.[5,6]

The symptoms of nasal polyposis include nasal obstruction and discharge, and impairment of sense of smell.[4] The objectives for the management of the condition include elimination or reduction in the size of polyps followed by reestablishment of an open nasal airway and nasal breathing, improvement or restoration of sense of smell, and ultimately prevention of polyp recurrence.[7] In nasal polyposis, topical nasal corticosteroids are considered the medical treatment of choice,[8] and several different intranasal corticosteroids have been investigated with regard to both effect on symptoms and reduction in polyp size.[7] These benefits may be attributed, at least in part, to the effect of topical corticosteroids on decreasing eosinophilic infiltration in the nasal mucosa.[9]

The objective of the present large, appropriately powered study was to evaluate the efficacy and safety of 200-µg doses of mometasone furoate nasal spray (NS) administered once daily (QD) in the morning or twice daily (BID) as monotherapy, compared with placebo, in the treatment of patients with nasal polyposis.

METHODS

STUDY DESIGN

This randomized, placebo-controlled, parallel-group, double-blind, multicenter study was conducted at 24 centers in 17 countries worldwide. The study was carried out in accordance with the Declaration of Helsinki, the US code of Federal Regulations, and guidelines on Good Clinical Practice. The study protocol and statement of informed consent (obtained from all subjects prior to study entry) were reviewed and approved by an institutional review board and independent ethics committee. The total study period ran from June 25, 2001 to January 20, 2003.

Subjects enrolled in the trial were at least 18 years old and had an endoscopically confirmed diagnosis of bilateral nasal polyps at the screening and baseline visits. Nasal polyps were graded as 1, 2, or 3 (on a scale of 0 to 3) in each of the right and left nasal cavities. In addition, subjects had to have clinically significant nasal congestion or obstruction, with a morning score of 2 or higher (on a scale of 0 to 3) for each of the last 7 days of a 14-day run-in period. Subjects with asthma were required to have a documented forced expiratory volume in 1 second of at least 80% of the predicted value within the 6 months prior to screening and no asthma exacerbations within the 30 days prior to screening. Subjects treated with inhaled corticosteroids were required to be taking a moderate, stable dose of no more than 800 μg/d of beclomethasone dipropionate or the equivalent for at least 1 month prior to screening and to remain with a stable dose throughout the study period.

Subjects were excluded from the study if they had a history of seasonal allergic rhinitis within the past 2 years, sinus or nasal surgery within the past 6 months, 3 or more nasal surgical procedures, or any surgical procedure that prevented accurate grading of polyps according to the study protocol. In addition, subjects were excluded if they had any of the following conditions: fibrotic nasal polyposis (based on endoscopic examination); complete or nearly complete nasal obstruction; nasal septal deviation requiring corrective surgery or nasal septal perforation; acute sinusitis, nasal infection, or upper respiratory tract infection at screening or in the 2 weeks prior to screening; ongoing rhinitis medicamentosa; Churg-Strauss syndrome or dyskinetic ciliary syndromes; cystic fibrosis; glaucoma or a history of posterior subcapsular cataracts; allergies to corticosteroids or aspirin; or any other clinically significant disease that could interfere with the evaluation of therapy. Use of concomitant medications that would interfere with study evaluations was not permitted, including nasal sodium cromolyn; nasal atropine or ipratropium bromide; corticosteroids (except permitted oral inhaled corticosteroids for asthma or mild or medium-strength corticosteroids for dermatologic purposes); antihistamines; decongestants; topical, oral, or ocular anti-inflammatory drugs; or topical, nasal, or oral antifungals. Use of acetaminophen (paracetamol) was encouraged for analgesic purposes, with nonsteroidal anti-inflammatory drug use limited to 5 consecutive days if alternative analgesia was required. Antibiotics were permitted for bacterial infection.

Subjects who met eligibility criteria at the screening visit (day −14, visit 1) underwent a 14-day, single-blind, placebo run-in period to help exclude placebo responders and identify subjects with stable disease. Eligible subjects at baseline (day 1, visit 2) were then randomized to receive 1 of 3 regimens: 200-μg mometasone furoate NS in the morning and matching placebo NS in the evening, 200-μg mometasone furoate NS in the morning and evening, or matching placebo NS in the morning and evening. Randomization was performed in blocks of 3 using random numbers generated by SAS function UNIFORM (SAS Institute, Cary, NC) with seed based on clock time. Randomization was stratified by the presence or absence of concurrent asthma. Subjects who presented with concurrent asthma were assigned randomization numbers in ascending sequential order using the lowest numbers available at the study center. Subjects without asthma were assigned randomization numbers in descending sequential order. Mometasone furoate NS was supplied as commercial Nasonex (Schering-Plough Corp, Kenilworth, NJ) in a metered-dose manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate calculated on the anhydrous basis. The aqueous medium contained glycerin, microcrystalline cellulose, carboxymethylcellulose sodium, sodium citrate, 0.25% w/w phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80.

Treatment was administered for 4 months in a blinded manner, with study visits on day 8 (visit 3) and months 1, 2, 3, and 4 (visits 4 to 7). Treatment compliance was evaluated at visits 3 through 7 by weighing each study drug bottle without the subject's knowledge. Unused study drug was collected at each visit.

EFFICACY ASSESSMENTS

The primary end points of the study were change from baseline to the end of the study (data from the last visit carried forward) in physician-evaluated bilateral polyp grade, calculated as the sum of grades in the left and right nasal cavities, and the change from baseline in subject-assessed congestion and/or obstruction averaged over the first month of treatment. Nasal endoscopy was performed by the physician at each visit, excluding visit 3, without using vasoconstrictors or decongestants. The size and extent of the polyps were graded on endoscopy as 0 (no polyps), 1 (polyps in the middle meatus, not reaching below the inferior border of the middle turbinate), 2 (polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate), or 3 (large polyps reaching below the lower inferior border of the inferior turbinate). Bilateral polyp grade was obtained as the sum of the individual grades for the left and right nasal cavities. Congestion and/or obstruction scores ranged from 0 (none) to 3 (severe). Subjects were instructed to evaluate their congestion and/or obstruction symptoms once a day in the morning before dosing, from screening until the end of treatment. Symptom evaluation reflected severity at the time of dosing (that is, instantaneous).

Secondary end points included changes from baseline for the following variables: symptoms of loss of smell, anterior rhinorrhea, and postnasal drip scores averaged over the first month of treatment and peak nasal inspiratory flow (PNIF) over months 1, 2, 3, and 4. Subjects scored their symptoms on a scale from 0 (none) to 3 (severe) each morning before dosing. Following this symptom assessment, they measured their PNIF each morning using a PNIF meter (Clement Clarke International Ltd, Harlow, England). In addition, the proportion of subjects demonstrating an improvement (defined as a reduction in bilateral polyp grade of ≥ 1 from baseline and a reduction in congestion and/or obstruction score of ≥ 0.5 from baseline) was recorded at the end point. The investigator also evaluated symptomatic therapeutic response at the end point using a scale of 0 (complete relief) to 4 (no relief).

SAFETY ASSESSMENTS

Safety variables included adverse event recording, laboratory tests, vital signs, and physical examination. Details of all reported adverse events were recorded throughout the study, with severity graded as mild, moderate, severe, or life-threatening, and the relationship to treatment determined by the investigator. Vital signs were measured at all visits. Clinical labora-

Table 1. Demographic and Medical History Details, Baseline Polyp Grade, and Symptom Scores

Characteristic	Mometasone Furoate Nasal Spray Dose 200 μg QD (n = 102)	200 μg BID (n = 102)	Placebo (n = 106)
Age, y			
Mean (range)	47.2 (18.0-86.0)	47.6 (21.0-74.0)	50.9 (21.0-76.0)
18 to <65	92 (90)	92 (90)	90 (85)
≥65	10 (10)	10 (10)	16 (15)
Male/female, %	70/30	62/38	65/35
Weight, mean (range), kg	74.2 (50.0-118.0)	73.8 (50.0-116.9)	75.4 (41.0-130.0)
Asthma history, No. (%)	15 (15)	19 (19)	17 (16)
Perennial allergic rhinitis history, No. (%)*	14 (14)	18 (18)	22 (21)
Bilateral polyp grade*	4.00	4.10	4.17
Congestion/obstruction score*	2.23	2.20	2.18
Loss of smell score*	2.03	1.94	1.96
Anterior rhinorrhea score*	1.53	1.58	1.57
Postnasal drip score*	1.47	1.46	1.41
PNIF, L/min*	102.1	95.4	97.7

Abbreviations: BID, twice daily; PNIF, peak nasal inspiratory flow; QD, once daily.
*Least squares mean values, obtained from analysis of variance with treatment, baseline asthma status, and treatment center effects.

tory tests and a physical examination were conducted at the screening visit (visit 1) and the last treatment visit (visit 7).

STATISTICAL ANALYSIS

Summaries of data were based on all randomized subjects (intent-to-treat principle). An analysis of variance was used to analyze responses for the efficacy end points, with stratification for sources of variability (treatment, center, and asthma status). Baseline bilateral polyp grade was added as a covariate to the analysis of variance model for analysis of the change from baseline in bilateral polyp grade (analysis of covariance) to account for any between-treatment baseline differences in this variable. Comparisons between treatment groups were based on differences in mean estimates from the analysis of variance or analysis of covariance models. All tests were carried out at the unadjusted significance level of alpha=.05.

It was determined that a total sample size of 100 subjects per treatment group would provide 90% simultaneous power at a 2-sided alpha level of .05 to detect a difference of at least 1.0 point in the change in bilateral polyp grade from baseline to the end point (assuming a standard deviation [SD] of 1.44) and of at least 0.37 points in the change in average congestion and/or obstruction score from baseline over the first month of treatment (assuming an SD of 0.8). With 100 subjects per treatment group, a difference of 0.66 in bilateral polyp grade would be detectable with 90% individual power.

RESULTS

SUBJECT CHARACTERISTICS

A total of 310 subjects were randomized to treatment. The 3 treatment groups were well matched with regard to baseline demographic and disease characteristics (**Table 1**). Small differences in baseline bilateral polyp grade were observed between treatment groups. Approximately 65% of subjects had a baseline bilateral polyp grade of 4 or more, and 85% to 88% of subjects had a moderate to severe baseline congestion/obstruction score.

Table 2. Number of Randomized Patients Who Completed or Discontinued Treatment and Reasons for Discontinuation*

Characteristic	Mometasone Furoate Nasal Spray Dose 200 μg QD	200 μg BID	Placebo
Randomized to treatment	102 (100)	102 (100)	106 (100)
Completed treatment	94 (92)	93 (91)	87 (82)
Discontinued treatment	8 (8)	9 (9)	19 (18)
Reasons for discontinuation			
Adverse event	0	0	1 (1)
Treatment failure	1 (1)	3 (3)	5 (5)
Lost to follow-up	0	0	2 (2)
Did not wish to continue	3 (3)	1 (1)	4 (4)
Noncompliance with protocol	2 (2)	3 (3)	1 (1)
Did not meet protocol criteria for entry	2 (2)	2 (2)	6 (6)

Abbreviations: BID, twice daily; QD, once daily.
*All data are reported as number (percentage) of subjects.

More than 85% of subjects completed the 4-month treatment period, with more than twice as many placebo recipients as active drug recipients discontinuing during the treatment phase (18% vs 8%). Reasons for discontinuation are summarized in **Table 2**. Approximately 90% of subjects were considered to be compliant with the dosing regimen (defined as using 59% to 138% of prescribed doses, according to medication bottle weight).

PRIMARY EFFICACY END POINTS

Treatment with 200 μg of mometasone furoate NS QD or BID produced a greater change from baseline to the end point in bilateral polyp grade than did placebo; this

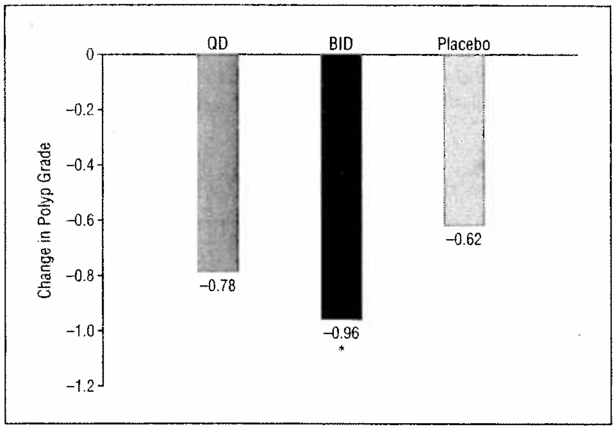

Figure 1. Change in mean bilateral polyp grade from baseline to the end point. Least square means and *P* values obtained from analysis of covariance with treatment, baseline asthma status, treatment center effects, and baseline bilateral polyp grade added as covariates. *End point* is defined as the last nonmissing reading for the subject. All mometasone furoate was administered as 200-μg doses of nasal spray. QD indicates once daily; BID, twice daily. Asterisk indicates $P<.05$ vs placebo.

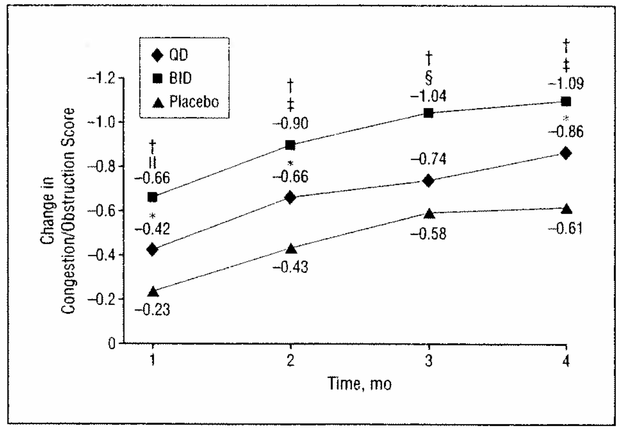

Figure 2. Change in mean congestion/obstruction score during the treatment period. Least square means and *P* values obtained from analysis of variance with treatment, baseline asthma status, and treatment center effects added as covariates. All mometasone furoate was administered as 200-μg doses of nasal spray. QD indicates once daily; BID, twice daily. Asterisk indicates $P<.05$ vs placebo; dagger, $P<.001$ vs placebo; double dagger, $P<.05$ vs QD dose; section mark, $P<.01$ vs QD dose; and parallel mark, $P\leq.001$ vs QD dose.

difference reached statistical significance with the BID dose ($P=.04$; **Figure 1**).

The BID dose was significantly superior to placebo in change from baseline in congestion/obstruction score over the primary time interval of 1 month ($P<.001$) and during the entire 4 months of treatment ($P<.001$; **Figure 2**). The QD dose also resulted in statistically significant changes in congestion/obstruction score compared with placebo at 1 month ($P=.01$), 2 months ($P=.02$), and 4 months ($P=.02$). Effects of treatment were observed as early as week 1 with BID dosing ($P<.001$ vs placebo) and week 2 with QD dosing ($P=.01$ vs placebo), with scores continuing to decrease over the course of the study. These results demonstrated a continued effect of treatment over time in both active treatment groups and in the placebo group, with the relative difference between both active treatments and placebo remaining relatively constant.

SECONDARY EFFICACY END POINTS

For the secondary end point of change from baseline in loss of smell averaged over the first month of treatment, the 200-μg BID dose of mometasone furoate NS demonstrated a statistically significant improvement over placebo ($P=.05$; **Figure 3**A). Furthermore, the BID dose maintained a numerically greater decrease from baseline in this symptom than placebo throughout the study (Figure 3B).

In addition, the BID dose resulted in statistically significant improvements over placebo for anterior rhinorrhea ($P<.001$) and postnasal drip ($P<.001$) at month 1 (Figure 3A), with improvements maintained at month 4 (Figure 3B). Statistically significant improvements relative to placebo were also seen for anterior rhinorrhea at all study time points after month 1 ($P\leq.004$) and for postnasal drip at all time points except month 3 ($P<.03$). Treatment with the QD dose also resulted in statistically significant improvements in anterior rhinorrhea over placebo at month 1 ($P=.02$; Figure 3A) and at all subsequent study time points except month 3.

Over the 4-month study period, the BID dose of mometasone furoate NS was statistically superior to the QD dose for anterior rhinorrhea at week 3, week 4, and month 1 of the study ($P\leq.02$) and for postnasal drip at week 2, week 3, and month 1 ($P\leq.03$).

Significant improvements in PNIF were measured in subjects receiving the BID dose at all time intervals ($P\leq.001$) and in those receiving the QD dose at week 2 and all subsequent time intervals ($P\leq.004$) compared with placebo (**Figure 4**). Subjects receiving the BID dose had greater improvements in PNIF than those receiving the QD dose at all time intervals, with the exception of week 2 ($P\leq.04$).

A significantly greater proportion of subjects receiving the BID dose (49%) met improvement criteria compared with those receiving either the QD dose (34%; $P=.03$) or placebo (25%; $P<.001$). Consistent with this finding, both active treatment groups were associated with significantly greater improvement in therapeutic response score (as assessed by investigators) at the end point compared with placebo ($P<.001$ for both groups).

SAFETY

Treatment with mometasone furoate NS was well tolerated and showed no unusual or unexpected events. Most adverse events were of mild or moderate intensity. The overall incidence of treatment-emergent adverse events was similar among the 3 treatment groups: 53%, 56%, and 51% in the QD, BID, and placebo groups, respectively. The most frequent treatment-emergent adverse events were upper respiratory tract infection, headache, and epistaxis (defined to include a wide range of bleeding episodes, from frank bleeding to bloody nasal discharge and flecks of blood in the mucus), with epistaxis being reported more frequently in the BID group (15% of subjects) than in the other groups (6% of QD subjects and 5% of placebo subjects). The incidences of upper respiratory tract infection and headache were simi-

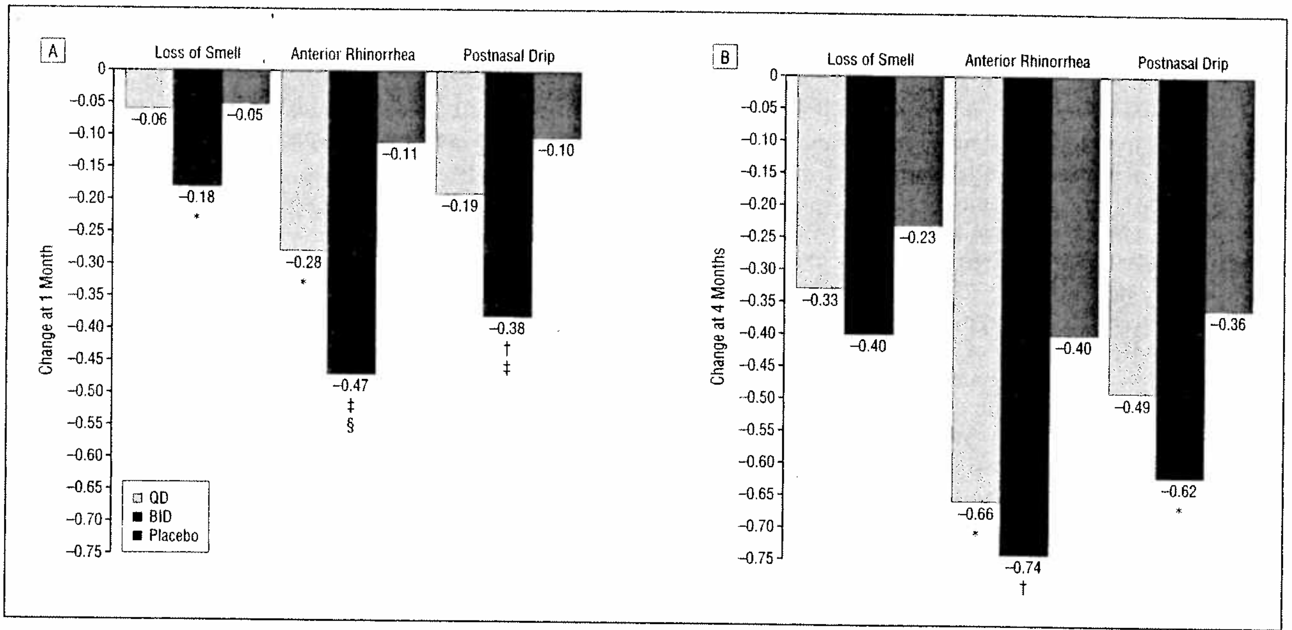

Figure 3. Change in mean individual symptom scores (loss of smell, anterior rhinorrhea, and postnasal drip) at month 1 (A) and month 4 (B) of the study period. Least square means and *P* values obtained from analysis of variance with treatment, baseline asthma status, and treatment center effects added as covariates. All mometasone furoate was administered as 200-μg doses of nasal spray. QD indicates once daily; BID, twice daily. Asterisk indicates $P<.05$ vs placebo; dagger, $P<.01$ vs placebo; double dagger, $P\leq.001$ vs placebo; section mark, $P<.05$ vs QD dose.

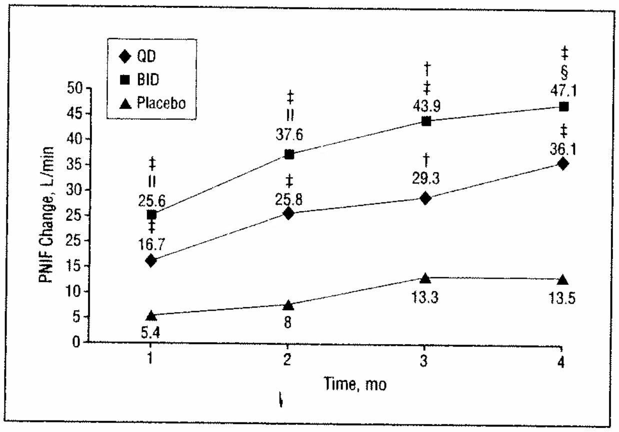

Figure 4. Change from baseline in mean peak nasal inspiratory flow (PNIF) during the treatment period. Least square means and *P* values obtained from analysis of variance with treatment, baseline asthma status, and treatment center effects added as covariates. All mometasone furoate was administered as 200-μg doses of nasal spray. QD indicates once daily; BID, twice daily. Asterisk indicates $P<.05$ vs placebo; dagger, $P<.01$ vs placebo; double dagger, $P\leq.001$ vs placebo; section mark, $P<.05$ vs QD dose; and parallel mark, $P<.01$ vs QD dose.

Table 3. Treatment-Related Adverse Events Occurring in 2% of Patients or More in Any Group*

	Mometasone Furoate Nasal Spray Dose		
Adverse Event	**200 μg QD (n = 102)**	**200 μg BID (n = 102)**	**Placebo (n = 106)**
Headache	1 (1)	5 (5)	2 (2)
Throat irritation	0	1 (1)	1 (1)
Pharyngitis	0	2 (2)	1 (1)
Upper respiratory tract infection	2 (2)	2 (2)	3 (3)
Overdose (not otherwise specified)	2 (2)	2 (2)	0
Epistaxis	4 (4)	13 (13)	5 (5)
Nasal burning	1 (1)	2 (2)	0
Nasal irritation	0	0	2 (2)

Abbreviations: BID, twice daily; QD, once daily.
*All data are reported as number (percentage) of subjects.

lar in all treatment groups. The most frequent treatment-emergent adverse events that were considered to be treatment-related are summarized in **Table 3**.

No deaths or life-threatening adverse events were reported. Serious adverse events were reported in 6 subjects, but these were considered to be unrelated to the study drug. Only 1 subject discontinued treatment because of an adverse event (a placebo recipient who experienced a severe loss of taste). Seven subjects interrupted randomized treatment because of an adverse event (1 QD subject, 3 BID subjects, and 3 placebo subjects). No clinically meaningful changes in laboratory parameters, vital signs, or limited physical examinations were noted in any treatment group.

COMMENT

The inflammatory processes underlying nasal polyposis are dominated by eosinophilic infiltration into the nasal mucosa and inhibition of eosinophil apoptosis.[10,11] This dysregulation of eosinophil function may be, at least in part, mediated through expression of inflammatory cytokines by T cells.[4]

In vitro studies indicate that corticosteroids may attenuate eosinophilic inflammation by inducing apoptosis.[12] Indeed, a series of small clinical trials has suggested that intranasal corticosteroids may reduce nasal polyp size and improve associated symptoms in subjects with nasal polyposis,[13-22] although this finding has yet to be validated in large, robust trials.

The present study was 1 of 2 similar trials designed to assess the efficacy and safety of 200-μg mometasone furoate NS QD or BID in nasal polyposis. Mometasone furoate is a potent, topically active, synthetic corticosteroid with anti-inflammatory activity. The NS formulation of mometasone furoate is used therapeutically and prophylactically in seasonal allergic rhinitis and therapeutically in perennial allergic rhinitis.[23-27]

The present study was conducted over a 4-month treatment period, chosen to allow for optimal assessment of treatment effect. It is recognized that, owing to the chronic inflammatory nature of the condition, change in polyp size is likely to be slow, a hypothesis supported by several small studies of the use of intranasal corticosteroids in nasal polyposis.[17,19,20] A parallel mometasone furoate NS study, conducted at sites in the United States and South America, is reported elsewhere.[28]

The primary end points in this study were change in bilateral polyp grade over the 4-month treatment period and change in congestion/obstruction score over the first month of treatment. It was important that the study was sufficiently powered to detect appropriate differences in both of these parameters, given that they appear to be disparate processes. Indeed, it has been shown that, although endoscopic nasal surgery reduces nasal polyp size, it has limited effect on perceived nasal obstruction and other symptoms,[4] presumably owing to the underlying inflammatory disease that contributes to symptoms.

After 4 months of treatment, both QD and BID doses produced numerically greater reductions in bilateral polyp grade compared with placebo. These differences reached statistical significance for the BID dose when analyzed using an analysis of covariance model. This model allowed for between-group differences in baseline polyp grade thus enhancing the precision of the measurement and has been used in other studies of intranasal corticosteroids for nasal polyposis.[22]

For the primary end point of change in congestion/obstruction score, both BID and QD doses produced statistically significantly superior improvements compared with placebo after 1 month and over the 4-month treatment period. Furthermore, the BID dose was significantly superior to the QD dose for this end point throughout the study from week 2 onward. These findings were supported by the objective measurements of PNIF recorded on a daily basis. Improvements in other symptoms such as sense of smell, postnasal drip, and anterior rhinorrhea were also observed with mometasone furoate NS.

The clinical significance of mometasone furoate NS is evident when the relative changes in polyp size and congestion/obstruction scores from baseline are examined. Considering that the mean baseline polyp grade was approximately 4, the 1-point change from baseline in polyp grade with the BID dose represents approximately 25% improvement. Likewise, the 0.5-point improvement in congestion/obstruction score from baseline with active treatment represents approximately a 22% improvement from the mean baseline score of 2.3.

The 2 doses selected for use in the study were based on the approved dose for the treatment of allergic rhinitis (200 μg QD). However, to account for possible hindrance of study drug distribution due to the mechanical obstruction of the polyps and because the condition itself may be less responsive to treatment than allergic rhinitis, a second dose (200 μg BID) was also investigated. The superior clinical efficacy of this BID dose seen for the primary end points is also supported by the significantly greater proportion of subjects who were classed as "improved" in the BID group compared with QD and placebo groups.

In this study, statistically significant improvements in polyp size and congestion/obstruction score were observed; thus, the proportion of subjects with improvement analysis is an appropriate means to further assess the clinical benefits of mometasone furoate NS in the treatment of polyposis. Indeed, approximately half of the subjects treated with the BID dose experienced a clinically meaningful change in both polyp size (≥1 point) and congestion/obstruction score (≥0.5 points). This represents almost twice the proportion of subjects considered improved compared with those who used placebo. As the definition of response is based on individual subject changes, these results further support the notion that BID treatment with 200 μg of mometasone furoate NS provides clinically meaningful benefits to patients with nasal polyposis.

It is also interesting to observe the large placebo effect seen in this study, possibly attributable to the nonactive aqueous solution in the NS. Such an effect has been observed in other studies of intranasal corticosteroids in nasal polyposis[15,20] and highlights the importance of including a placebo group in such studies to ensure that a true measure of treatment benefit can be attained.

Reported compliance with the dosing regimen in this study was high (approximately 90%); however, it should be noted that bottle weight as a means of measuring compliance is limited by variability in individual bottle weights and by the potential for nonadherent subjects to actuate the device to improve reported compliance.

Both doses of mometasone furoate NS were well tolerated. The most frequently reported adverse events were epistaxis (which included a wide range of bleeding episodes, from frank bleeding to flecks of blood in the mucus) and headache, a finding that is consistent with data from clinical trials in the treatment of allergic rhinitis.[23-27] There is often concern within the medical community with regard to long-term use of corticosteroids, particularly in terms of impact on bone density, hypothalamic pituitary-adrenal axis suppression, and the development of cataracts or glaucoma. Although the effects of mometasone furoate NS on bone density have not been formally studied, systemic absorption of mometasone furoate NS is negligible and is unlikely to have an effect on this marker: even at 20 times the recommended daily allergic rhinitis dose, mometasone furoate NS has no adverse effect on urinary-free cortisol and plasma cortisol levels or on suppression of the hypothalamic pituitary-adrenal axis.[28] Furthermore, reports of glaucoma or cataracts with intranasal corticosteroid use are few.[29]

In conclusion, the results of this randomized, placebo-controlled trial demonstrate that mometasone furoate NS is an effective and well-tolerated treatment for patients with bilateral nasal polyposis. As such, it is the first intranasal corticosteroid to be approved by the US Food and Drug Administration for first-line medical treatment of nasal polyposis.

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Correspondence: Pär Stjärne, MD, PhD, Department of Otorhinolaryngology, Karolinska University Hospital, 14186 Stockholm, Sweden (par.stjarne@karolinska.se).
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ORIGINAL ARTICLE

The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study

PÄR STJÄRNE[1], KARIN BLOMGREN[2], PER CAYÉ-THOMASEN[3], SIRKKU SALO[4] & TOR SØDERSTRØM[5]

[1]*Karolinska University Hospital, Stockholm, Huddinge, Sweden,* [2]*Helsinki University Central Hospital, Helsinki, Finland,* [3]*Gentofte University Hospital of Copenhagen, Copenhagen, Denmark,* [4]*Turun Korvacenter Oy, Turku, Finland and* [5]*Allergologisk Poliklikk, Bergen, Norway*

Abstract

Conclusion. In subjects with mild-to-moderate nasal polyposis, treatment with mometasone furoate nasal spray (MFNS) 200 μg once daily (QD) significantly decreases nasal congestion, reduces polyp size, and improves quality of life. *Objectives.* To evaluate the efficacy and safety of MFNS, administered QD in the morning, in subjects with mild-to-moderate nasal polyposis. *Subjects and methods.* This randomized, double-blind, double-dummy, placebo-controlled clinical trial enrolled subjects with mild-to-moderate nasal polyposis at 12 centers in Denmark, Finland, Norway, and Sweden. Inclusion criteria were: age $\geq$18 years, a diagnosis of bilateral nasal polyps, and clinically significant nasal congestion. Following a 2–4-week run-in period, subjects were randomized to receive MFNS 200 μg QD or matching placebo for 16 weeks. *Results.* A total of 298 subjects were randomized to treatment. Of those subjects included in the intent-to-treat efficacy analysis ($n = 291$), a statistically greater proportion of the MFNS group than the placebo group had improvements in investigator-assessed nasal congestion score between baseline and end point (the primary outcome) (74.3% vs 46.8%; $p < 0.001$). Significant benefits of MFNS were also seen for secondary end points, including polyp size, sense of smell, peak nasal inspiratory flow, therapeutic improvement, and quality-of-life measures. MFNS was well tolerated, with no unusual or unexpected adverse events.

Keywords: *Intranasal corticosteroid, nasal congestion, nasal polyp, olfaction, rhinorrhea, quality of life, mometasone furoate*

Introduction

The characteristic symptoms of nasal polyposis include nasal congestion and nasal discharge, with more than 75% of subjects experiencing impairment or loss of sense of smell as a consequence of their disease [1]. A study of individuals with nasal polyposis found that health-related quality of life (QoL) scores on the Short-Form 36 questionnaire were significantly worse than those of individuals with perennial allergic rhinitis [2], indicating that the symptoms of nasal polyposis can have a marked impact on subjects' QoL.

Nasal polyposis is often associated with asthma, aspirin sensitivity, or cystic fibrosis. The pathophysiology of the condition remains unclear, although it is thought to involve inflammation of the nasal mucosa dominated by eosinophilic infiltration [1]. Inflammation in nasal polyposis is also characterized by the release of cytokines, such as interleukin (IL)-3, IL-5, granulocyte–macrophage colony-stimulating factor, and interferon-γ, which inhibit apoptosis of eosinophilic granulocytes [3,4]. These inflammatory processes ultimately lead to blockage of the paranasal sinuses, and the formation of polyps. Bacterial colonization of the nasal cavity, resulting in the synthesis and release of enterotoxins that aggravate inflammation, may also play a role [5].

The treatment objectives in nasal polyposis are to reduce or eliminate polyps, open the nasal airway, improve or restore the sense of smell, and prevent recurrence of nasal polyps [6]. Although surgery is often used to improve aeration of the sinuses and

Correspondence: Pär Stjärne, MD, PhD, Department of Otorhinolaryngology, Karolinska University Hospital, Huddinge, 14186 Stockholm, Sweden. Tel: +46 858587340. Fax: +46 707250749. E-mail: par.stjarne@karolinska.se

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allow recovery of the nasal mucosa, disparities have been observed between the effects of surgical treatment on polyp score and symptom relief [7]. In particular, surgery appears to have a very limited effect on olfactory dysfunction.

Medical treatment is recommended as a first step for polyposis treatment [1,6]. Topical and systemic corticosteroids are typically regarded as the mainstay of medical management of nasal polyposis, and act to reduce edema, inflammation, and hyperreactivity [1,6,8–14].

Mometasone furoate is a potent, topically active, synthetic corticosteroid with anti-inflammatory activity. The nasal spray formulation of mometasone furoate (mometasone furoate nasal spray; MFNS) has been shown to be efficacious and well tolerated, with minimal systemic activity, in a series of clinical trials in subjects with seasonal or perennial allergic rhinitis [15–18]. Furthermore, MFNS 200 μg, administered once (QD) or twice daily, produced statistically significant reductions in nasal polyp size and congestion/obstruction score, relative to placebo, over a 4-month treatment period in two large, randomized, controlled trials in subjects with mild-to-moderate bilateral polyposis [19,20].

The objective of this study was to evaluate the efficacy and safety of MFNS 200 μg, administered QD, in the morning, in subjects with mild-to-moderate nasal polyposis. The impact of treatment on QoL was also investigated.

Subjects and methods

Study design

This randomized, double-blind, double-dummy, placebo-controlled trial enrolled subjects at 12 centers in Denmark, Finland, Norway, and Sweden. Inclusion criteria were: age ≥ 18 years; a diagnosis of bilateral nasal polyps; and clinically significant nasal congestion. Nasal congestion was defined as significant when the symptom score was ≥ 2 (on a scale of 0–3, see *Efficacy assessments*, below) for ≥ 4 days per week during the month before screening, at screening, and at the baseline visit. Exclusion criteria included: nasal polyp surgery within the 6 months before screening; unhealed nasal surgery or trauma; polyp size of 3 (on a scale of 0–3, see *Efficacy assessments*, below); the presence of polyps that could interfere with nasal spray application; and significant nasal structural abnormalities. Subjects were also excluded if they had ongoing concurrent nasal infections, glaucoma with narrow anterior chamber angle of the eye, rhinitis medicamentosa, or hereditary mucociliary dysfunction. Concomitant medications that might interfere with study evaluations were prohibited during the treatment period. These included: nasal atropine or ipratropium bromide; corticosteroids (except permitted inhaled corticosteroids for asthma or topical corticosteroids for dermatological purposes); antihistamines; decongestants; and leukotriene receptor antagonists. Devices that dilate the nostrils to improve nasal breathing were also prohibited. Oxymetazoline drops were permitted as rescue medication for intolerable nasal symptoms for a maximum of 7 consecutive days and a total of ≤ 10 days during the treatment period.

Subjects who met the eligibility criteria at the screening visit (visit 1) underwent a 2–4-week no-treatment run-in period. They were subsequently randomized at the baseline visit (day 0, visit 2) according to a computer-generated code to receive MFNS 200 μg QD in the morning or a matching placebo spray. The randomization schedule for the blinded treatments was maintained by the sponsor and only disclosed after the study was completed and the database closed. The MFNS was supplied in a metered-dose manual pump spray unit containing: an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate, calculated on the anhydrous basis in an aqueous medium containing glycerin; microcrystalline cellulose and carboxymethylcellulose sodium; sodium citrate; 0.25% w/w phenylethyl alcohol; citric acid; benzalkonium chloride; and Polysorbate 80. The placebo aqueous nasal spray was formulated to match MFNS exactly, except for the active ingredient.

Subjects received treatment for 16 weeks. Follow-up visits were scheduled on days 28 (visit 3), 56 (visit 4), 84 (visit 5), and 112 (visit 6). Treatment compliance was assessed at each visit by asking the subject whether the study drug had been taken as instructed, and by reviewing the diary cards.

All subjects gave written, informed consent to participate in the study, which was carried out in accordance with the Declaration of Helsinki and applicable laws, regulations, and the principles of good clinical practice.

Efficacy assessments

The primary efficacy end point was the proportion of subjects with an improvement in investigator-assessed nasal congestion score between baseline and either the study end point or the last visit for which data were available. Nasal congestion score was evaluated on a scale of 0–3, as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe. Improvement was defined as a decrease in score of ≥ 1 point.

Secondary end points included the proportion of subjects with an improvement in nasal polyp size and investigator-assessed sense of smell and rhinorrhea score between baseline and the end of the study, where an improvement was defined as a decrease of ≥ 1 point in score. Additional secondary end points included the proportion of subjects with a change in peak nasal inspiratory flow (PNIF), treatment response score, and olfactory threshold between baseline and the end of the study.

Polyp size was measured endoscopically in both nostrils and graded as 0 (no polyps), 1 (polyps in the middle meatus, not reaching below the inferior border of the middle concha), 2 (polyps reaching below the inferior border of the middle concha, but not below the inferior border of the inferior concha), and 3 (large polyps reaching below the lower inferior turbinate or polyps medial of the middle concha). The grade for the more severely affected nostril was recorded. Rhinorrhea was assessed using the same scale as that used for nasal congestion, while sense of smell was graded as 0 (normal), 1 (slightly impaired), 2 (moderately impaired), or 3 (absent). Improvements in sense of smell and rhinorrhea were defined as decreases of ≥ 1 point on the symptom score scales. Treatment response was graded as 0 (complete relief: virtually no symptoms), 1 (marked relief: symptoms greatly improved and scarcely troublesome), 2 (moderate relief: symptoms present and may be troublesome, but noticeably improved), and 3 (treatment failure: no relief, deterioration, or no change in symptoms). Olfactory threshold was determined using butanol in dilutions ranging from 4% to 0.000008%. The olfactory threshold was identified when the subject was able to distinguish the same butanol concentration from a blank control on five consecutive attempts.

Polyp size, symptoms (congestion, rhinorrhea, sense of smell), PNIF, and response to treatment were measured at all study visits, and olfactory threshold was determined at visits 1, 2, 5, and 6.

Subject perceptions of treatment outcomes were assessed using daily diaries. The severity of rhinorrhea and nasal congestion was measured using the four-point scale described previously. Subjects were instructed to evaluate their symptoms twice a day based on their status over the past 12 h, and to note the use of study drugs, rescue medication, and concomitant medication.

Scores for QoL were recorded at every study visit using an investigator-administered scale consisting of the following items: distribution between mouth and nose breathing (1 = mostly mouth, 2 = equal, 3 = mostly nose); experience of smell and taste (1 = almost not at all, 2 = fair, 3 = very good); experience of interference with daily activities caused by nasal symptoms (0 = none, 1 = mild, 2 = moderate, 3 = severe); and experience of sleep disturbance caused by nasal symptoms (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Safety assessments

Safety variables included adverse events, vital signs, and the results of physical examinations. Details of all reported adverse events were recorded throughout the study, with severity graded as mild, moderate, or severe. The relationship between adverse events and the assigned treatment was determined on the basis of the investigator's judgment. Vital signs were measured at all visits, and physical examinations were carried out at screening (visit 1) and at the final study visit (visit 6).

Statistical methods

All analyses and summaries are based on the intent-to-treat (ITT) population, which included all randomized subjects who received at least one dose of study medication and for whom one baseline and one post-baseline measurement were obtained.

For categorical variables (proportion of subjects with change in symptom score, polyp grade, and QoL variables), comparisons between treatment groups were made using Cochran-Mantel-Haenszel χ^2 tests taking stratification by center into account. Other secondary variables (PNIF, olfactory threshold, subject-assessed symptom scores, and therapeutic response score) were compared using analysis of variance (ANOVA).

It was determined that a total sample size of 125 subjects per treatment group would provide 90% power to reject the null hypothesis of equal proportions of subjects with improvement, performing a two-sided test at the 5% significance level.

Results

Subject characteristics

A total of 298 subjects were randomized to treatment. The study population was predominantly male, and >75% of subjects had a nasal polyp score of ≥ 2. No clinically relevant differences were observed in demographic characteristics or in baseline symptom scores between the two treatment groups (Table I). In total, 296 subjects received at least one dose of study medication and were included in the safety analyses; and 291 subjects received at least one dose of study medication and underwent one baseline and one post-baseline assessment, allowing for inclusion in the ITT population for the efficacy analyses. The other seven subjects did not receive any study medication or did not have any appro-

Table I. Demographic details, baseline symptom scores, and polyp size for each treatment group (all randomized subjects).

Parameter	MFNS 200 μg QD ($n = 153$)	Placebo ($n = 145$)
Mean age, years (range)	53 (24–84)	53 (20–86)
Male/female (%)	74.5/25.5	71.7/28.3
>2 nasal surgeries, *n* (%)	39 (25.5)	38 (26.2)
Smokers, *n* (%)	35 (22.9)	26 (17.9)
Nasal congestion score, *n* (%)		
1 (Mild)	2 (1.3)	1 (0.7)
2 (Moderate)	120 (78.4)	117 (80.7)
3 (Severe)	31 (20.3)	27 (18.6)
Rhinorrhea score, *n* (%)		
0 (None)	44 (28.8)	33 (22.8)
1 (Mild)	44 (28.8)	64 (44.1)
2 (Moderate)	51 (33.3)	36 (24.8)
3 (Severe)	14 (9.2)	12 (8.3)
Sense of smell score, *n* (%)		
0 (Normal)	17 (11.1)	10 (6.9)
1 (Slightly impaired)	30 (19.6)	31 (21.4)
2 (Moderately impaired)	43 (28.1)	52 (35.9)
3 (Absent)	63 (41.2)	52 (35.9)
Polyp size, *n* (%)		
1	38 (24.8)	34 (23.4)
2	100 (65.4)	85 (58.6)
3	15 (9.8)	26 (17.9)
Mean PNIF (L/min)	102.19	96.68
Mean olfactory threshold	2.96	3.46

QD, once daily; PNIF, peak nasal inspiratory flow.

priate baseline/post-baseline data and were therefore excluded from analysis.

Of the 298 subjects randomized to treatment, 235 (78.9%) completed the study. Premature withdrawals were more common in the placebo group than in the MFNS group (30.3% vs 12.4% of subjects, respectively). Reasons for discontinuation are summarized in Table II.

Approximately 10% of subjects were considered to be noncompliant with the dosing regimen (defined as missing study medication doses for >7 consecutive days up to a maximum of 10 days, using rescue medication for >10 days during treatment, or using prohibited concomitant medications).

Efficacy

Investigator-assessed nasal congestion score improved from baseline to end point (reduction of ≥ 1 point in score) in a greater proportion of MFNS recipients (74.3%) than placebo recipients (46.8%; $p < 0.001$; Figure 1). The beneficial effects of MFNS remained significant compared with placebo in all subgroups when analyzed according to age and gender. A greater proportion of the MFNS-treated group than the placebo group also experienced an improvement from baseline to end point in polyp size (reduction of ≥ 1 point) (41.4% vs 26.6% of subjects, respectively; $p = 0.003$). In addition, significantly more MFNS than placebo recipients demonstrated improvements from baseline to end point in investigator-assessed sense of smell and rhinorrhea scores ($p = 0.007$ and $p = 0.004$, respectively; Figure 1).

The mean increase in PNIF from baseline to end point was significantly greater with MFNS than with placebo (+22 L/min vs +10 L/min, respectively; $p = 0.025$). MFNS recipients also were more likely to report complete, marked, or moderate relief in

Table II. Reasons for discontinuation of treatment.

Parameter	MFNS 200 μg QD ($n = 153$)	Placebo ($n = 145$)
Subjects discontinuing treatment	19 (12.4%)	44 (30.3%)
Reasons for discontinuation		
Adverse event	1 (0.7%)	4 (2.8%)
Treatment failure*	8 (5.2%)	27 (18.6%)
Treatment failure/noncompliance with protocol*	0	1 (0.7%)
Significant intercurrent illness	0	2 (1.4%)
Did not wish to continue	2 (1.3%)	0
Noncompliance with protocol*	4 (2.6%)	6 (4.1%)
Other†	4 (2.6%)	4 (2.8%)

*Five subjects with 'treatment failure' or 'noncompliance with protocol' cited as the reason for discontinuation also had adverse events that were recorded as possibly contributing to their discontinuation.

†Includes: prohibited concomitant medication use (one MFNS, one placebo); did not receive study medication (one placebo); did not meet inclusion/exclusion criteria for nasal congestion score (one MFNS, two placebo); stopped taking study medication (one MFNS); and visit dates outside accepted ranges (one MFNS).

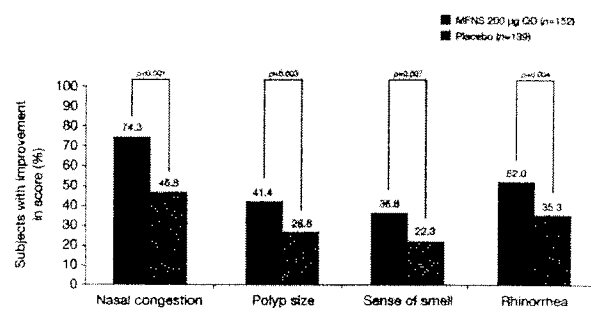

Figure 1. Proportion of subjects with an improvement in investigator-assessed symptom score or polyp size at end point compared with baseline. Improvement was defined as a change of ≥ 1 point in symptom score or polyp size. Pairwise comparisons were analyzed by Cochran-Mantel-Haenszel test with treatment and site effects.

terms of therapeutic response ($p < 0.001$ for overall response; Figure 2). A trend for improvement in mean olfactory threshold with MFNS compared with placebo was observed (+0.90 vs +0.83, respectively), although this did not reach statistical significance.

Over the entire treatment period, subject-reported daily symptoms of nasal congestion, rhinorrhea, and sense of smell were significantly better in the MFNS group than in the placebo group ($p \leq 0.005$).

Improvements in QoL parameters were recorded for a greater proportion of MFNS than placebo recipients (Figure 3). These differences reached statistical significance for nose breathing ($p < 0.001$), interference with daily activities ($p = 0.003$), and sleep disturbance ($p = 0.001$), with a trend for improvement seen in taste and smell.

According to subject diaries, treatment with MFNS also resulted in significantly less use of rescue medication, with 34.2% of MFNS recipients and 50.7% of placebo recipients receiving at least one dose of rescue medication ($p = 0.006$).

Safety

In this study, MFNS was well tolerated, being associated with no unusual or unexpected events (Table III). Of the subjects included in the safety analysis ($n = 296$), adverse events, which may or may not have been related to the study medication, were reported in 94 of the MFNS recipients (61.4%) and 67 of the placebo recipients (46.9%). Most of these adverse events were considered by the investigators to be of mild or moderate intensity.

Adverse events considered by the investigators to be possibly, probably, or definitely related to the study medication occurred in 29 subjects receiving MFNS (19%) and 19 subjects receiving placebo (13.3%). The most frequently reported treatment-related adverse event was epistaxis (defined to

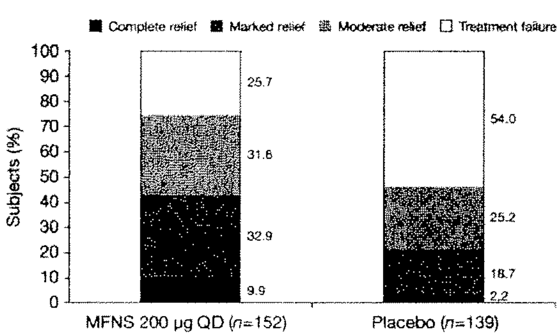

Figure 2. Therapeutic response to treatment evaluated at end point. Analysis of overall therapeutic response by ANOVA with treatment and site effects found that MFNS demonstrated significantly superior effects to placebo ($p < 0.001$).

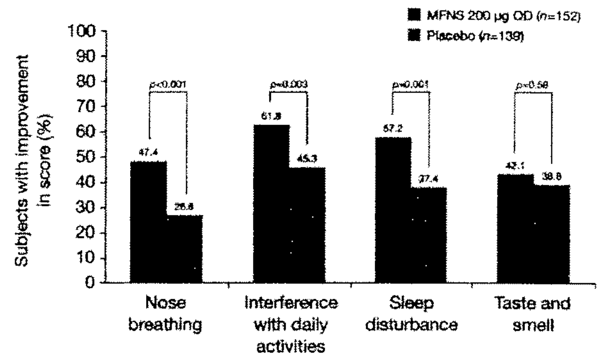

Figure 3. Proportion of subjects with an improvement in QoL parameters at end point compared with baseline. Improvement was defined as a change of ≥1 point in score. Pairwise comparisons were analyzed by Cochran-Mantel-Haenszel test with treatment and site effects.

include a wide range of bleeding episodes, from frank bleeding to bloody nasal discharge to flecks of blood in mucus), which occurred in 13.1% and 4.9% of MFNS and placebo recipients, respectively. All incidences of treatment-related epistaxis were of mild intensity, with the exception of one moderate event in the placebo group.

No deaths were reported during this study. Of the seven treatment-emergent adverse events classified as severe, only one was considered to be probably related to the study medication (nasal irritation in a placebo recipient). Serious adverse events, all of which were considered to be unrelated to the study drug, were reported by eight subjects. Ten subjects discontinued treatment because of adverse events (three subjects in the MFNS group and seven subjects in the placebo group), although, for five of these, another primary reason was also recorded for discontinuation (Table II). In addition, the investigator interrupted randomized treatment (which was then resumed) because of an adverse event in a further five subjects (two in the MFNS group and three in the placebo group). No clinically relevant changes in vital signs or physical examinations were noted in either group.

Table III. Treatment-emergent adverse events occurring in ≥5% of subjects in either group.

Adverse event	MFNS 200 µg QD ($n = 153$)	Placebo ($n = 143$)
Upper respiratory tract infection	45 (29.4%)	31 (21.7%)
Epistaxis	21 (13.7%)	6 (4.2%)
Headache	16 (10.5%)	5 (3.5%)
Sore throat (not otherwise specified)	4 (2.6%)	8 (5.6%)

Discussion

The results of this Nordic study demonstrate that MFNS 200 µg QD is efficacious and well tolerated in subjects with mild-to-moderate nasal polyposis. Over the 16-week course of the study, an improvement in investigator-assessed nasal congestion score of ≥ 1 was recorded in almost 75% of MFNS recipients, compared with fewer than half of placebo recipients. This finding is of considerable clinical significance, given that nasal obstruction has been identified as the most common primary symptom of polyposis [21]. Corresponding improvements in subject-evaluated symptoms with MFNS underscore the clinical importance of the results.

Improvements in objective parameters of polyposis, such as reduction in polyp size and improvement in PNIF, were also reported with MFNS. Furthermore, significant improvements in investigator-evaluated rhinorrhea and sense of smell were observed with active treatment.

In this study, MFNS was well tolerated. Adverse events were consistent with those reported in clinical trials of MFNS in the treatment of allergic rhinitis [15–18].

A high placebo response was observed in this study, with almost half of placebo recipients experiencing an improvement in the primary end point. This beneficial effect of placebo treatment has also been demonstrated in previous studies with nasal steroid formulations [8,10], and may be caused by the introduction of fluids into the nasal cavity on a regular basis [10]. The placebo spray used in this study comprised exactly the same formulation as MFNS, but without the active ingredient; therefore, the differential between the effect of MFNS and placebo should accurately reflect the additional benefit of treatment. This is further supported by the much higher rate of subjects considered to have failed treatment (according to investigator-assessed therapeutic response) in the placebo group (54%) than in the active treatment group (25%). The finding that a quarter of the subjects who received active treatment were considered treatment failures may reflect the fact that some subjects – generally those with more severe polyps – require treatment with oral steroids or surgery to obtain relief from symptoms [22].

It is interesting to note that, in addition to the objectively measured clinical benefits, treatment with MFNS improved QoL parameters, such as nasal breathing, interference with daily activities, and sleep disturbances. These positive exploratory QoL findings warrant further investigation with validated generic and disease-specific tools.

Endoscopic sinus surgery has been shown to reduce polyp size and nasal blockage in subjects with nasal polyposis [23]; however, there is a paucity of data directly comparing the benefits of surgery with medical therapy. One small study comparing systemic and local corticosteroid therapy alone (one nostril) and in conjunction with endoscopic sinus surgery (the other nostril) has shown that while the reductions in polyp size following surgery are long-lasting, polyp score did not show any relation to symptom score [7]. In particular, surgery did not have any additional effect on sense of smell. This may be because eosinophilic inflammation, caused by an underlying mucosal pathology, contributes towards the symptoms of the condition to a greater degree than volume changes in the nasal cavity [24]. Topical corticosteroids have been shown in vitro to stimulate eosinophilic apoptosis [25]. It is thought that this effect translates into the clinical benefit of reducing inflammation in the nasal cavity of patients with nasal polyposis, and may explain the efficacy of MFNS in relieving the symptoms of nasal polyps.

In conclusion, the results of this multicenter, randomized, placebo-controlled clinical trial demonstrate that MFNS 200 µg, administered QD in the morning, is well tolerated, improves nasal congestion and other symptoms, and reduces polyp size in subjects with mild-to-moderate nasal polyposis.

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The role of topical nasal steroids in the treatment of children with otitis media with effusion and/or adenoid hypertrophy

S. Cengel*, M.U. Akyol

Hacettepe University, Faculty of Medicine, Otorhinolaryngology Head-Neck Surgery, 06100 Ankara, Turkey

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KEYWORDS
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Summary

Objectives: Topical steroid treatment can be a powerful alternative to surgery in controlling adenoid hypertrophy and otitis media with effusion (OME).
Methods: A prospective, controlled, randomized, clinical study in an academic tertiary care center. A total of 122 children (3—15-year-old) on the waiting list for an adenoidectomy and/or ventilation tube placement were enrolled into the study and control groups. The study group (67 patients with adenoid hypertrophy, 34 of them with otitis media with effusion) received intranasal mometasone furoate monohydrate 100 mcg/day, and the control group (55 patients with adenoid hypertrophy, 29 of them with otitis media with effusion) was followed up without any treatment. All patients were evaluated at 0 and 6 weeks. The assessment of each patient included history, a symptom questionnaire, a skin prick test, a tympanogram, if possible a pure tone audiogram, and otoscopic and endoscopic examinations. The size of adenoid tissue was graded as a percentage according to obliteration of the choanae. The adenoid/choana ratio (A/C) was recorded for each patient. Symptoms were scored as 0 (absent), 1 (intermittent/periodic), or 2 (continuous). The data were analyzed with the "Statistical Package for the Social Sciences" (SPSS 9.0) using the appropriate nonparametric tests for nominal and ordinal data.
Results: Resolution of otitis media with effusion in the study group (42.2%) was significantly higher than that in the control group (14.5%) ($p < 0.001$). Forty-five patients (67.2%) with adenoid hypertrophy in the study group showed a significant decrease in adenoid size according to the endoscopic evaluation compared to the control group ($p < 0.001$). A significant improvement in obstructive symptoms was seen in the study group ($p < 0.001$). The endoscopically measured adenoid/choana ratio and degree of obstructive symptoms showed a significant correlation ($r = 0.838$ $p < 0.001$, $r = 0.879$ $p < 0.001$, $r = 0.838$ $p < 0.001$, $r = 0.879$ $p < 0.001$). The adenoid/choana ratio improved significantly in atopic patients in the study group

* Corresponding author. Tel.: +90 312 3051785; fax: +90 312 311 35 00.
E-mail address: senemcengel@hotmail.com (S. Cengel).

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($p < 0.05$), whereas in atopic patients in the control group there was no change ($p = 0.221$).
Conclusion: Nasal mometasone furoate monohydrate treatment can significantly reduce adenoid hypertrophy and eliminate obstructive symptoms. It is a useful alternative to surgery, at least in the short term, for otitis media with effusion.

1. Introduction

Adenoidal hypertrophy (AH) and otitis media with effusion (OME) are the most frequent indications for surgery in children. The current treatment options for OME include eliminating the risk factors, following up without treatment, use of antibiotic and/or decongestant medication, maneuvers to open the Eustachian tubes, such as with nasal balloons, prophylactic antibiotic use and, if medical treatment fails, tympanostomy tube placement with or without adenoidectomy [1,2]. In the case of adenoidal hypertrophy, non-surgical alternatives are limited to adjunctive treatment of co-existing upper airway infections.

Recently, a potential role of corticosteroids in the treatment of both diseases has emerged [3,4]. Short-term use of systemic steroids provides a temporary improvement but long-term use of systemic steroids is not appropriate in children due to severe side-effects. On the other hand, topical nasal steroids without systemic side-effects might be used [5].

In this controlled randomized prospective study of children with adenoidal hypertrophy and/or otitis media with effusion unresponsive to antibiotic treatment and waiting for surgery, the efficacy of intranasal mometasone furoate monohydrate was determined in comparison with a control group over 6 weeks of therapy.

2. Materials and methods

2.1. Study design

A prospective, controlled, randomized, clinical study in an academic tertiary care center, Hacettepe University Hospital's Otorhinolaryngology Department, between October and June, in 2002—2003.

As the study was designed to have no connection with any of the manufacturers of the drugs or the pharmaceutical industry at all, it was not possible to obtain a placebo, and therefore the study could not be double blinded. The randomization process involved enrolling every second patient in the waiting list into the treatment and control groups consecutively. However, this method sometimes failed as some of the families did not want their children to be in the groups that they had been placed in and the patients were therefore included in the other group. However, the bias that occurred due to this occasional failure of the randomization process was not thought to influence the validity of the study.

2.2. Patients

A total of 122 children (3—15-year-old) on the waiting list for adenoidectomy and/or ventilation tube placement were enrolled into the study and control groups. There were no statistical differences between in groups in terms of age, sex, presence of atopy, family history or previous medical history. There was also no difference between in groups in the term of season during the study. The institutional ethics committee had given approval for the study and informed consent for participation was obtained from the parents. The study group (67 patients with AH, 34 of them with OME) received intranasal mometasone furoate monohydrate 100 mcg/day, one spray in each nostril once a day for 6 weeks by the technique of neck flexion while dispensing from a vertically held bottle in order to direct the spray toward the posterior nasal cavity. The control group (55 patients with AH, 29 of them with OME) was followed up without any treatment. No other medication was allowed during the study in either group.

The criteria for OME in the study were as follows: (1) documented persistent middle ear effusion by otoscopic examination for a minimum of 3 months at the time of entry into the study, (2) middle ear pressure less than -150 mm H_2O, and conductive hearing loss in audiometry supporting the diagnosis of OME and (3) treatment with appropriate antibiotics at least twice before. Each ear was evaluated separately during the study. The criterion for adenoidal hypertrophy was chronic nasal obstruction unexplained by any reason other than adenoidal hypertrophy.

Subjects were excluded if they met any of the following criteria: (1) previous use of systemic or intranasal steroids, (2) surgery for these illnesses, (3) active upper airway infections in the previous 2 weeks, (4) history of immunodeficiency, hypersensitivity to mometasone furoate monohydrate, or any systemic and local contraindication against corticosteroids, and (5) a craniofacial anomaly.

2.3. Evaluations and patient management

All patients were evaluated at 0 and 6 weeks. Assessment of each patient included history, a symptom questionnaire, a skin prick test, a tympanogram, if possible a pure tone audiogram, an otoscopic examination and an endoscopic examination. All the examinations of the patients were carried out by the authors of the paper, therefore the examiners were not blinded. The ears were examined separately by otoscopy for tympanic membrane appearance and mobility was assessed by pneumatic otoscopy. A middle ear pressure less than −150 mm H_2O and Jerger type B flat tympanogram were considered to support the diagnosis of OME. Conductive-type hearing loss was also thought to indicate the presence of effusion. Tympanometry and audiometry were performed by a certified audiologist in the Industrial Acoustic Company standardized rooms by Greson-Steadler GSIG1 clinical audiometry and interacoustics AT22, AT23, AT27 tympanometry using a TDH-39 earlap. Adenoidal hypertrophy and the upper airway were evaluated by flexible endoscopy (Karl Storz 1101-RPI) by one of the authors and any pathology other than adenoid tissue that can cause obstructive symptoms was excluded. Endoscopy was tolerated well by all patients. The size of adenoid tissue was graded as a percentage according to obliteration of the choanae. The adenoid/choana ratio (A/C) was recorded for each patient. The symptom questionnaire was filled in at initial enrollment and after 6 weeks. It consisted of a parental assessment of the patient's ear pain, ear popping, hearing loss, nasal obstruction, nasal discharge, snoring, mouth breathing, and apnea. The obstructive symptoms were scored as 0 (absent), 1 (intermittent/periodic), or 2 (continuous). Subsequently, the scores of each patient were added up

Table 1 Distribution of the patients and improvement rates in the groups

	Study group (week 0)		Study group (week 6)	Control group (week 0)		Control group (week 6)	Total
Male		27			25		52
Female		40			30		70
Age (year)		3–15			3–13		
Mean		6.9			6		
OME	64		37	55		47	$p < 0.001$**
		$p < 0.05$*			$p = 0.5$*		
A/C ratio	80		40	70		80	
Median (%)		$p < 0.001$*			$p = 0.013$*		$p < 0.001$**
Mouth Breathing	Absent 7		23	8		11	$p < 0.001$**
	Intermittent 11		34	21		12	
	Continuous 49		10	26		32	
		$p < 0.001$*			$p > 0.05$*		
Snoring	14		42	11		13	$p < 0.001$**
	16		20	20		11	
	37		5	24		31	
		$p < 0.001$*			$p > 0.05$*		
Nasal obstruction	9		37	17		14	$p < 0.001$**
	21		26	20		19	
	37		4	18		22	
		$p < 0.001$*			$p > 0.05$*		
Nasal discharge	56		63	47		47	—
	8		4	8		7	
	3		0	0		1	
Apnea	44		58	40		38	$p < 0.001$**
	14		6	8		9	
	9		3	7		8	
		$p < 0.001$*			$p > 0.05$*		

* Statistics within the same group.
** Statistics between the study and control groups.

and the overall score was used for comparison at the end of the study. Each symptom was also compared separately between two evaluations. Skin prick tests against tree, grass and mold extract mixes, olives, cat and dog fur, Dermatophagoides pteronyssinus and farinae dust mites were used. The patient was considered atopic if a positive skin test was associated with a positive history.

2.4. Statistical analysis

The data were analyzed with the ''Statistical Package for the Social Sciences'' (SPSS 9.0) using the appropriate nonparametric tests for nominal and ordinal data: McNemar test, Wilcoxon signed-rank test, Mann—Whitney *U*-test, Spearman's rho test, and chi-square test.

3. Results

Table 1 summarizes the patient's ages, sexes, and improvements in OME, A/C ratio and obstructive symptoms according to group at entry and at the end of the study. There were 63 patients with OME in the study. Hearing loss (according to parents' responses) was present in 39 patients (61.9%) and ear pain in 16 patients (25.4%). All patients with OME had type B tympanograms and the mean bone-air gap in the audiogram (500—4000 Hz) was 21 dB at entry. OME was present in 34 patients in the study group (50.7%) and in 29 patients in the control group (52.7%). Thirty patients in the study group and 26 in the control group had bilateral OME, whereas 4 patients in the study group and 3 in the control group had unilateral EOM (64 ears in the study group and 55 ears in the control group).

The rate of the resolution of OME in the study group (42.2%) was significant higher than that in the control group (14.5%) ($p < 0.001$).

Symptom scores of patients treated with intranasal steroid were also significantly improved at the end of study ($p < 0.001$). There were no significant improvements in the control group ($p = 0.134$). Improvements in the study group were significantly higher than those in the control group ($p < 0.001$).

There were no significant differences in the A/C ratios of the patients with or without OME at the beginning of the study in either group ($p = 0.116$). There was also no significant difference in the improvement degree of the A/C ratio between the patients with resolved OME and those with unresolved OME in the study group.

The correlation between obstructive symptom scores and adenoid/choana ratio (A/C ratio) measured by endoscopy was statistically significant in both groups in the first and consecutive evaluations ($r = 0.838$ $p < 0.001$, $r = 0.879$ $p < 0.001$ in the study group and $r = 0.838$ $p < 0.001$, $r = 0.879$ $p < 0.001$ in the control group).

A/C ratios were graded as grade I (0—25%), II (26—50%), III (51—75%) and IV (76—100%) to make measurements more objective. The graded results of A/C ratios are given in Tables 2 and 3 according to group. There was also a statistically significant improvement in the graded A/C ratio of the study group ($p < 0.001$). Although 39 patients (58.2%) were evaluated as grade IV at entry, 12 patients (17.9%) remained at this grade after treatment with intranasal steroid. Twenty-eight patients (40%) showed complete improvement according to both A/C ratio and symptoms. The overall A/C ratios of 45 patients (67.2%) showed regression to a lower grade. This improvement in the A/C ratio in the treatment group was statistically significant when compared with the control group ($p < 0.001$). Patients who did not improve after nasal steroid treatment were operated on as planned before.

As the A/C ratios of the patients decreased with treatment the obstructive symptoms improved in group 1, whereas neither the A/C ratios nor the obstructive symptoms improved in the control group ($p < 0.001$).

The frequency of atopy diagnosed by history and prick test was 8.9% (6/67) in the study group and 9% (5/55) in the control group. The resolution rate of OME did not show any difference between atopic and non-atopic patients in either group ($p = 0.607$ in the study group and $p = 0.377$ in the control group). Atopic patients in the study group showed significant

Table 2 Adenoid/choana ratios in the study group ($p < 0.001$)

Last A/C ratio	First A/C ratio				*N*
	I	II	III	IV	
I	5	2	1	2	10
II		4	15	10	29
III			1	15	16
IV				12	12
n	5	6	17	39	67

Table 3 Adenoid/choana ratio in the control group ($p = 0.118$)

Last A/C ratio	First A/C ratio				*N*
	I	II	III	IV	
I	7				7
II		4	4		8
III			9		9
IV			11	20	31
n	7	4	24	20	55

improvements in the A/C ratio ($p < 0.05$), whereas atopic patients in the control group did not show any difference ($p = 0.221$).

4. Discussion

Adenoidal hypertrophy obstructing the nasal airway in children may cause severe symptoms and complications, such as enuresis, retardation in cognitive and physical development, and cardio-respiratory disorders [6,7]. Otitis media with effusion, which causes hearing loss, affects language and speech acquisition [8]. Furthermore, it may cause chronic middle ear sequelae, such as retraction of the tympanic membrane, leading to cholestatoma formation and permanent hearing disorders [9].

Adenoidectomy has been the treatment of choice in cases of adenoidal hypertrophy and its related symptoms [7,10]. Nonsurgical approaches other than adenoidectomy are limited to medical treatment of co-existing upper airway infections. On the other hand, the treatment of OME is still unclear due to its multi-factorial pathogenesis, usually including Eustachian tube dysfunction, upper airway infections, chronic inflammation, and allergy. In addition, environmental factors, such as daycare, passive smoking and feeding habits contribute to the pathogenesis [2,11,12]. Prophylactic antibiotic use and avoidance of environmental risk factors are commonly suggested treatment options as many studies have reported bacterial colonization with β-lactamase activity in middle ear effusion [13]. Decongestants and antihistamines have no proven effect in the treatment in the absence of allergy [14]. Insertion of tympanostomy tubes, with or without adenoidectomy, has been shown to be effective globally in the treatment/control of persisting middle ear effusion [1].

Systemic corticosteroids produce a prompt, temporary decrease in adenoid size and resolution in middle ear effusion but significant side-effects cause avoidance of its chronic use in children [3–5]. Compared with systemic steroids, topical nasal steroids have limited systemic effects and would be expected to exert their anti-inflammatory effects locally on the nose, nasopharynx, and Eustachian tube [15,16]. While systemic steroids have been extensively studied, the topical nasal steroids as the sole treatment of OME and adenoid hypertrophy have not been adequately evaluated.

Oral steroids stabilize membrane phospholipid breakdown and prevent the formation of inflammatory mediators. They also promote shrinkage of peritubular lymphoid tissue, enhance secretion of Eustachian tube surfactant, and reduce the viscosity of middle ear fluid [15,17,18]. By these mechanisms, they aid middle ear resolution. Reduction in adenoid size may be due to a direct lympholytic action and to a general anti-inflammatory effect in respiratory tissues [17,19,20]. Relief of nasal obstruction occurs as a result of decreased inflammation and reduction of adenoid size. An additional cause may be decreased significance of the adenoid tissue as a reservoir for infection. In contrast to oral steroids, topical steroids exert their effects only locally, therefore having limited systemic side-effects.

Several reports have analyzed the value of oral corticosteroids or the combination of oral corticosteroids with antibiotics in the treatment of OME [3,4,20]. Macknin and Giebink reported 15% and 45% cure rates respectively with the use of oral steroids alone [21,22]. In other studies using combinations of prednisone and antibiotics, cure rates have ranged from 40% to 77% [20–22]. In addition to studies of oral steroids, a limited number of studies have addressed topical nasal steroid use in persistent middle ear effusion. In 1980, Schwartz reported a 48% cure rate in an uncontrolled trial of beclomethasone in 25 children after 5 weeks of treatment without concurrent antibiotics [23]. Lindholdt and Kortholm in 1982 reported no difference between active and placebo groups in a blinded, placebo-controlled study of beclomethasone administered for 1 month in 70 children [24]. In both studies, children did not have enough previous follow up to allow a decision concerning the presence of persistent middle ear effusion. Shapiro in 1982 compared dexamethasone nasal spray to placebo in a blinded study of 45 children with a minimum of 4-week duration. In first 3 weeks, dexamethasone showed more efficacy than the placebo but in the third week there was no difference between them [25]. In contrast to these studies, Tracy et al. in 1998 reported a double-blind, placebo-controlled randomized study of nasal beclomethasone [18]. Patients were randomized into three groups: (1) prophylactic antibiotics, (2) prophylactic antibiotics plus intranasal beclomethasone and (3) prophylactic antibiotics plus intranasal placebo. The beclomethasone plus antibiotics group improved more rapidly than did the others.

In our study, topical steroids were used in the treatment of OME as the only medication for 6 weeks, and 42.2% of the patients recovered completely. All the patients before participating in our study had undergone 3 months of follow up for OME and during this period they received antibiotic therapy at least twice. Patients unresponsive to antibiotic treatment and waiting for surgery were included in the study. Therefore, the 42.2% recovery rate without any other simultaneous medication appears more significant. Another important point is that recovery occurred in patients in whom medical therapy had failed and who were scheduled for surgery.

The role of topical nasal steroid use has also been evaluated in the treatment of adenoid hypertrophy. Demain and Goetz in 1995 reported a double blind, placebo-controlled crossover study of standard dose aqueous nasal beclomethasone in the treatment of 17 patients with adenoid hypertrophy [17]. An 82% reduction in the mean nasal obstruction symptom score accompanied a 29% mean reduction in the adenoid/choana ratio. Another study, in 2003, reported a 45% cure rate in nasal obstruction after 2 weeks of beclomethasone treatment [26]. Low dose treatment continued until 24 weeks and the need for adenotonsillectomy decreased to 53% in these patients at the end. Brouillette et al. in 2001 studied nasal fluticasone in pediatric obstructive sleep apnea patients and reported a decrease in the number of obstructive and mixed apnea and hypopnea [27]. However, the size of adenotonsillar hypertrophy was not regressed significantly. In our study, 28 patients (40%) showed complete improvement according to both the A/C ratio and symptoms. The overall A/C ratios of 45 patients (67.2%) showed regression to a lower grade. As the patients' A/C ratios decreased with treatment, the obstructive symptoms also improved.

One of the main problems of nasal steroid therapy is the duration and dosage because there is no consensus in the literature. The dose used in our study for AH and OME is equal to that used in allergic rhinitis in the prescription of the drug. The safety of at least 1-year long use of topical steroids for children with allergic rhinitis is well known in the literature. Therefore, we think that long-term nasal steroids can be used in a routine dose for adenoid hypertrophy and otitis media with effusion.

Our study concerns the short-term follow-up of the patients. The demonstrated efficacy of the topical steroid treatment in the control of OME and nasal obstruction due to AH during its use does not give us any hint about the duration of this control. Therefore, the middle- (months) and long-term (years) effects of the drug in the control of OME and AH must be studied. In order to determine the long-term efficacy of the drugs, patients in the study group that recovered underwent a 1-year follow-up. The results are planned to send separately when we are enough data.

Endoscopy is an accurate and reproducible method for repeated assessments of adenoid size. This dynamic type of assessment of nasal airway obstruction by adenoidal hypertrophy correlates more closely than static radiographic methods [28,29]. Flexible endoscopy was safe and tolerated well by the pediatric patients. There were no complications during this study. The A/C ratio accurately describes adenoid size. The endoscopically measured A/C ratio and degree of obstructive symptoms showed significant correlations at every step of our study.

In the literature, many studies show that OME and AH occur more frequently in allergic children [30,31]. In our study, 9% of the patients were shown to be allergic. There is no difference in the response to nasal steroid treatment between allergic and non-allergic patients with respect of OME. However, in the case of AH we found a statistical difference between the allergic and non-allergic patients' responses to the treatment, in favor of the allergic patients. In the literature, treatment responses vary. Due to the limited number of allergic patients in our study we cannot draw a strong conclusion about the effects of topical steroids in this subgroup of patients.

5. Conclusion

Resolution of OME in the study group (42.2%) was significantly higher than that in the control group (14.5%) ($p < 0.001$). Forty-five patients (67.2%) with adenoid hypertrophy in the study group showed significant decreases in adenoid size according to the endoscopic evaluation compared to the control group ($p < 0.001$). A significant improvement in obstructive symptoms was seen in the treatment group ($p < 0.001$). These results indicate that nasal mometasone furoate monohydrate treatment can significantly reduce adenoid hypertrophy and obstructive symptoms. It seems to be a useful alternative to surgery for OME. However, these results are only short-term; a long-term follow-up is necessary.

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Mometasone Furoate Nasal Spray in Seasonal Allergic Rhinitis

Effective in Relieving Ocular Symptoms

by Eric Schenkel, Craig LaForce, & Davis Gates

Background: Mometasone furoate nasal spray (MFNS) is effective for preventing and treating nasal symptoms in seasonal allergic rhinitis (SAR). Its effects on ocular symptoms have not been investigated. This retrospective analysis examined the effects of MFNS on ocular symptoms in subjects with SAR.

Methods/Data base: Ocular symptom data were pooled and analyzed from four randomized, double-blind studies comparing MFNS 200 mcg once daily (n = 494) with placebo (n = 497). Subject-reported ocular itching, redness, and tearing were recorded at baseline and twice daily throughout treatment on a scale of 0 (none) to 3 (severe). Total ocular symptom score (TOSS) was defined as the combined 2-week average symptom scores.

Results: MFNS produced a statistically greater reduction in TOSS from baseline as compared to placebo (−1.33 vs. −0.94, $p < 0.05$). Likewise, mean 2-week reductions in individual symptoms were significantly improved with MFNS ($p < 0.05$ for each symptom). In subjects with TOSS ≥ 4 at baseline, MFNS recipients (n = 298) reported a significantly greater reduction in TOSS as compared to placebo recipients (n = 304; −1.97 vs. −1.51, $p < 0.05$), with statistically significant benefits also observed in individual ocular symptoms ($p < 0.05$ for each symptom).

Conclusions: MFNS has a beneficial effect on ocular symptoms, in addition to its established effects on nasal symptoms, in subjects with SAR.

Keywords: seasonal allergic rhinitis, mometasone furoate, nasal spray, intranasal corticosteroid, ocular symptoms

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Introduction

Seasonal allergic rhinitis (SAR), or hay fever, is the most common allergic disease in the United States, and is estimated to occur in approximately 10% of the population [1]. The condition is characterized by the classic nasal symptoms of sneezing, nasal itching, clear rhinorrhea, and nasal congestion [2] during the defined season in which aeroallergens (such as tree, weed, and grass pollens, and outdoor mold spores) are abundant. Many patients with SAR manifest allergic conjunctivitis, resulting in ocular tearing, itchiness, and redness [3]. These symptoms have a notable impact on patient quality of life, as patients with bloodshot, itchy, and watery eyes due to SAR have a higher degree of pain and discomfort compared with age- and gender-matched controls [4].

Intranasal corticosteroids are recommended for preventing and treating nasal symptoms in patients with allergic rhinitis, but have been thought to have little effect on ocular symptoms [2]. However, preliminary studies have suggested that intranasal corticosteroids may also have a beneficial effect on eye tearing, redness, and itching [5–8].

Mometasone furoate is an antiinflammatory intranasal corticosteroid that is indicated for the prevention and treatment of SAR symptoms, including nasal congestion [9–14]. The effects of once-daily mometasone furoate nasal spray (MFNS) in alleviating ocular symptoms in subjects with a history of SAR were investigated in this retrospective analysis.

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TABLE 1
DEMOGRAPHIC CHARACTERISTICS AND BASELINE OCULAR SYMPTOM SCORES FOR ALL RANDOMIZED SUBJECTS

	MFNS 200 mcg once daily (n = 494)	Placebo (n = 497)
Mean age, years (range)	30.1 (12–71)	30.2 (12–71)
Gender, male (%)	244 (49.4%)	249 (50.1%)
Race, Caucasian (%)	429 (86.8%)	438 (88.1%)
Mean (± SD) TOSS	4.42 ± 2.06	4.57 ± 2.13
Mean (± SD) eye itch score	1.68 ± 0.74	1.72 ± 0.77
Mean (± SD) eye redness score	1.35 ± 0.81	1.40 ± 0.79
Mean (± SD) eye tearing score	1.39 ± 0.77	1.45 ± 0.81

MFNS = mometasone furoate nasal spray;
TOSS = total ocular symptom score

TABLE 2
BASELINE OCULAR SYMPTOM SCORES FOR SUBJECTS WITH BASELINE TOSS ≥ 4.0

	MFNS 200 mcg once daily (n = 298)	Placebo (n = 304)
Mean (± SD) TOSS	5.77 ± 1.29	5.95 ± 1.28
Mean (± SD) eye itch score	2.12 ± 0.49	2.18 ± 0.48
Mean (± SD) eye redness score	1.81 ± 0.62	1.83 ± 0.57
Mean (± SD) eye tearing score	1.83 ± 0.54	1.93 ± 0.58

MFNS = mometasone furoate nasal spray; TOSS = total ocular symptom score

Material and Methods

Subjects

The four source studies included in this analysis were conducted in accordance with the Declaration of Helsinki and guidelines on Good Clinical Practice, and in compliance with Institutional Review Board requirements. Written informed consent was obtained from each subject, or subject's caregiver if the subject was aged < 18 years, prior to beginning any study-related procedures. The safety and efficacy of MFNS in treating the nasal symptoms of SAR in the source studies were reported elsewhere; results for specific ocular symptoms were not reported [9–14].

Subjects were eligible for inclusion in the source studies if they were ≥ 12 years of age with a ≥ 2-year history of SAR, as documented by a positive response to a skin-prick test (defined as a wheal diameter ≥ 3 mm larger than the diluent control) to a prevailing aeroallergen. Subjects were required to be symptomatic at baseline and screening. Exclusion criteria included significant metabolic, cardiovascular, neurologic, hematologic, respiratory, or renal disease, or any other clinically significant disease that could interfere with the study schedule or evaluation of SAR. Subjects who were pregnant, had asthma requiring inhaled or systemic corticosteroids, or had clinically significant upper respiratory or sinus infection were also excluded from study participation.

Study design

This is a retrospective analysis of pooled data from four randomized, double-blind, placebo-controlled clinical trials evaluating the efficacy and safety of MFNS in subjects with SAR. Subjects were included in the pooled analysis if their change in ocular symptoms from baseline to endpoint was large enough to be evaluated; subjects were chosen randomly without regard to degree of symptomatic improvement.

Following a 3-day run-in period, subjects were randomly assigned to MFNS 200 mcg once daily or matching placebo spray for 14 days in three of the studies and 28 days in the fourth study. In the 28-day study, only data from the first 14 days of treatment were evaluated for the purpose of this analysis. Subjects assessed the effects of treatment on the ocular symptoms of SAR (itching, redness, and tearing) on a scale of 0 (none) to 3 (severe) in the morning (AM) and evening (PM) during the run-in and treatment periods. Scores were recorded in subjects' diaries for investigator review. Total ocular symptom score (TOSS) was defined as the combined 2-week average AM and PM scores for each symptom.

Statistical analysis

Ocular symptom score data were pooled from the four studies. To account for any differences between the four studies in the baseline symptom scores, the analyses for ocular symptoms included baseline score as a covariate in inferential analyses of the pooled studies. As a minimum ocular symptom score was not an inclusion criterion, reliable estimates of change and percent change from baseline were difficult to provide. Therefore, a subgroup analysis was performed on subjects with a baseline TOSS of ≥ 4. The 2-week average change from baseline in ocular symptom score was analyzed using an analysis of covariance (ANCOVA) model that included treatment and study as fixed effects and baseline ocular symptom score as a covariate. The baseline score was defined as the average of the AM and PM evaluations for the 3 days before the morning of the first dose and the AM evaluation prior to the first dose. Patients without a post-baseline evaluation of ocular symptoms were excluded. Least-square means and p values of treatment differences were obtained from the output of the ANCOVA.

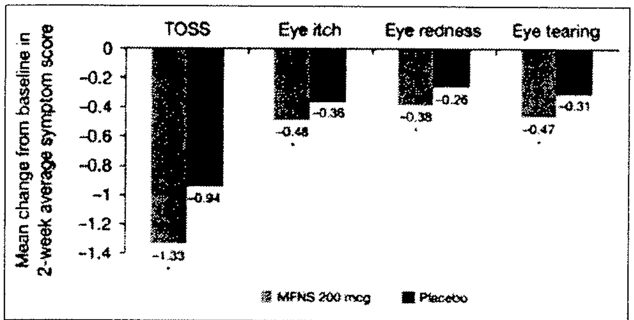

Figure 1. Mean 2-week change from baseline in total and individual ocular symptom scores for all randomized subjects ($p < 0.05$ vs. placebo; MFNS = mometasone furoate nasal spray; TOSS = total ocular symptom score).

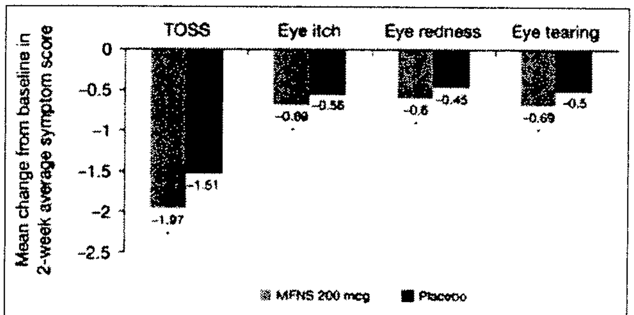

Figure 2. Mean 2-week change from baseline in total and individual ocular symptom score for subjects with total ocular symptom score ≥ 4 at baseline ($p < 0.05$ vs. placebo; MFNS = mometasone furoate nasal spray; TOSS = total ocular symptom score).

Results

A total of 991 subjects received MFNS 200 mcg once daily (n = 494) or placebo (n = 497). Demographic characteristics were similar among treatment groups, with a mean baseline TOSS of 4.42 for the MFNS group and 4.57 for the placebo group (see Table 1). Three subjects in the MFNS group and five in the placebo group did not have ocular symptom data at baseline and/or endpoint and were therefore not included in this analysis. Among the 61% of subjects with a TOSS ≥ 4 at baseline, mean baseline score was 5.77 for MFNS recipients (n = 298) and 5.95 for placebo recipients (n = 304; see Table 2).

In the total study population, MFNS was associated with significantly greater reductions from baseline in the 2-week average TOSS than placebo (–1.33 vs. –0.94, –29.8% vs. –5.6%, $p < 0.05$). Over 2 weeks, the MFNS treatment group reported significantly greater overall mean reductions in the ocular symptom scores for itching, redness, and tearing than the placebo group ($p < 0.05$; see Figure 1).

In the subgroup of subjects with a baseline TOSS of ≥ 4, MFNS recipients reported a significantly greater reduction in the 2-week average TOSS than the placebo recipients (–1.97 vs. –1.51, –32.3% vs. –25.0%, $p < 0.05$). Statistically significant improvements were also seen for the mean 2-week average individual symptom scores in the MFNS subgroup compared with the placebo subgroup ($p < 0.05$; see Figure 2).

MFNS was well tolerated in all studies. The most common treatment-related adverse events were headache (reported by 5% of subjects in each treatment group), pharyngitis (3% in the MFNS group vs. 2% in the placebo group), nasal burning (2% vs. 3%, respectively), and sneezing (1% vs. 3%, respectively).

Discussion

Intranasal corticosteroids are considered a mainstay of treatment for allergic rhinitis [2, 15]. Many studies have shown the effectiveness of these antiinflammatory agents for treating congestion and other nasal symptoms in SAR [9–14, 16–23]; however, only recently have their effects on ocular symptoms been considered [5, 6].

Ocular redness, tearing, and itching were measured in four similarly designed clinical studies of MFNS in patients with SAR, and data from these studies were pooled to determine the effects of MFNS in alleviating ocular symptoms. In this analysis, MFNS 200 mcg once daily was shown to be effective in relieving total and individual ocular symptoms in subjects with SAR. Given that ocular symptoms are notably bothersome to patients with SAR [4], the statistically significant reduction in TOSS with MFNS over 2 weeks is likely to be clinically significant.

Because a minimum ocular symptom score was not an inclusion criterion in any of the four studies, estimating change and percentage change from baseline provided a challenge, as a small change from a baseline score close to zero results in a large percentage change that is unlikely to be representative of the treatment effect. However, in the subgroup analysis of subjects with a baseline TOSS of ≥ 4, statistically significant improvements in total and individual ocular symptoms were seen with MFNS compared with placebo. A TOSS of ≥ 4 was chosen as a cutoff for the subgroup analysis because subjects with a TOSS ≥ 4 had to have a score ≥ 2 (moderately severe symptom) on at least one of the three ocular symptom scores; scores ≥ 2 were considered indicative of symptoms which were sufficiently severe for evaluation of improvement. This result confirmed that MFNS monotherapy has a beneficial effect in subjects with moderate or severe ocular symptoms, and supports the use of MFNS in subjects experiencing ocular symptoms associated with SAR. Although the small sample size reduced the likelihood of detecting statistically significant differences for each study, meaningful estimates of a treatment effect could be determined for this subgroup. The effect size for each symptom was about 0.15, which is similar to what has been reported for other treatments of allergic disorders [24].

The exact mechanism by which intranasal corticosteroids improve ocular symptoms has not been elucidated. A plausible explanation proposes that intranasal corticosteroids reduce swelling and inflammation at the nasolacrimal duct, thereby improving drainage and reducing the concentration of allergen within the conjunctiva [6]. This hypothesis is supported by another retrospective analysis of data from the four studies described in this report. This analysis found that MFNS produced highly significant reductions in nasal congestion score ($p < 0.001$) compared with placebo after 2 weeks of therapy, even in subjects with severe congestion symptoms at baseline [25]. Alternatively, it has been shown that allergic inflammation in one organ of the body can influence the physiologic activity of other sites in the body through neuronal reflex activity [26]. The reduction in nasal inflammatory mediators with MFNS could affect reflex neuronal activity that reduces allergy manifestations at other sites.

In conclusion, this analysis suggests that MFNS 200 mcg, administered once daily, has a beneficial effect on ocular symptoms in subjects with SAR, even those with moderate or severe symptoms at treatment initiation. This finding is in addition to its established effects on nasal symptoms.

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Eric Schenkel (to whom correspondence should be addressed) is with the Valley Clinical Research Center, 3729 Easton-Nazareth Highway, Suite 202, Easton, PA 18045, USA (tel. +1 610 252-7388, e-mail ESchenkelm@aol.com). Craig LaForce is with the University of North Carolina School of Medicine, Raleigh, NC, USA. Davis Gates is with the Schering-Plough Research Institute, Kenilworth, New Jersey, USA.